REMARKS

The Office Action has been carefully reviewed. No claim is allowed. Claims 1, 3-11 and 13-31 presently appear in this application and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

The interview among Mr. Browdy and Dr. Yun, representing applicants, and Examiner Wehbé, on October 29, 2002, is hereby gratefully acknowledged. Applicants' representatives wish to thank the examiner for the courtesies extended during this interview. It is hoped and believed that the outstanding enablement issues will be overcome by the claims as amended and the evidence submitted with this amendment. The arguments presented at the interview are also incorporated hereinbelow.

The rejection of claims 1, 3-11, and 13-31 under 35 U.S.C. §112, first paragraph, for lack of enablement has been maintained in part. The examiner states that applicants' arguments have been fully considered but have not been considered persuasive in overcoming the following instant grounds of rejection as indicated below.

1. The issue that the skilled artisan would not have predicted success in making HbsAg particles which encapsulate a hydrophobic or insoluble protein or peptide using the described methodology of incubating the two ingredients in aqueous solution (Office Action of June 5, 2002, paragraph bridging pages 3 and 4).

This part of the rejection is respectfully traversed. In the present claims, the antigenic molecule, regardless of whether or not it is hydrophobic, is recited in the alternative as being either "entrapped within the interior of an HBsAg particle" or "exposed or present at the surface of an HBsAg particle". Therefore, an antigenic molecule need not be required to be both entrapped within the interior of an HBsAg particle and exposed or present at the surface of an HBsAg particle; only satisfying one of the alternatives for being carried on an HBsAg particle is sufficient to satisfy the enablement provision of 35 U.S.C. §112, first paragraph.

A declaration executed by Jorg Reimann, a co-inventor of the present invention, is attached hereto for the examiner's consideration. Applicants request that this declaration be fully considered after a final rejection pursuant to 37 CFR §1.116(c), because applicants state that although the experiments were initiated prior to the June 5, 2002, mailing date of the final Office Action, the results were not completed and analyzed until after June 5, 2002. Consequently, the attached declaration could not have been filed prior to the mailing of the final Office Action.

The REIMANN declaration presents results in Exhibit A which clearly show that HBsAg particles loaded with a hydrophobic antigenic peptide using the methodology disclosed in the instant specification stimulated or enhanced a CTL response to the antigen over any CTL response to the HBsAg particle alone or to

the antigenic peptide alone. This stimulated or enhanced CTL response is dose dependent on the amount of loaded antigenic peptide. Claim 1 is now amended to recite "stimulating or enhancing" instead of "stimulating or modulating" a CTL response to make clear that the presently claimed method boosts (enhances) the level of an existing CTL response, i.e., a weak CTL response, or stimulates a CTL response where it is negligible or nonexistent with the antigenic molecule alone.

2. The issue of unpredictability of stimulating or modulating a CTL response to any antigen using any route of administration (Office Action of June 5, 2002, end of first paragraph).

This part of the rejection is respectfully traversed. The present invention is directed to stimulating or enhancing a CTL response. Those in the art of immunization are highly skilled in eliciting an immune response and would well appreciate what route of administration would be suitable for the purpose of stimulating or enhancing a CTL response. If the examiner finds it more acceptable to use the language "by an effective route" in the claims, applicants are willing to amend the claims accordingly.

3. The issue of unpredictability in generating an immune response because the working example with IL-2 in the specification shows that HBsAg particles encapsulating IL-2 were ineffective in generating a HBsAg CTL response (Office Action of June 5, 2002, second paragraph on page 5).

This part of the rejection is respectfully traversed. In the REIMANN declaration, Tables 1 and 2 show the entrapment and bioactivity (% from theoretical bioactivity) of,

respectively, IL-2 and IFNα (another representative immunostimulating molecule), with different entrapment methods. The results in Table 1 demonstrate that IL-2 was effectively encapsulated into HBsAg particles without impairing its biological activity (encapsulation procedures B and H were the most effective in obtaining biologically active IL-2-loaded HBsAg particles). These results provide support for a previously presented argument that the specification's working example regarding IL-2 failed to show CTL response only because of unsuccessful loading conditions which led to inactivation of the cytokine. However, by applying the same methodology (i.e., mere mixing and incubation of the two ingredients) at a less aggressive temperature (e.g., room temperature in procedure B instead of 45°C) the IL-2 loaded into the particle retained its bioactivity.

Since IL-2 has already been associated in the literature with CTL response (as also admitted by the examiner on page 5, second paragraph, of the Office Action of June 5, 2002), it is highly expected that the biologically active IL-2-loaded HBsAg particles as discussed above are also immunostimulating *in vivo*.

Table 2 and Exhibit B are further provided in the REIMANN declaration as a showing that other representative immunostimulating molecules, i.e., IFNα and immunostimulatory ODN, are effective in stimulating or enhancing a CTL response when loaded onto HBsAg particles.

4. The issue that, while the specification teaches that the purpose of stimulating an immune response such as a CTL response is for vaccination against infectious organisms such as viruses or bacteria, the specification does not provide evidence that stimulating a CTL response would result in protection or treatment of an infection.

This part of the rejection is respectfully traversed. At the time the invention was made, one of skill in the art would recognize that there is a correlation between CTL responses and disease treatment. As evidence thereof, attached to the Reimann declaration are three articles, Exhibits E1, E2 and E3, from among numerous articles in the field describing such a correlation.

As to the examiner's statement that previous Office Actions have provided evidence in the form of teachings by Yasutomi et al. and Fox et al. that the skilled artisan at the time of filing did not consider the generation of CTL responses as correlative of disease treatments, particularly viral disease, Fox teaches on page 128, first column, that CTLs appear to play a prominent role in maintaining the relative health of most HIV-infected individuals who do not progress to full-blown AIDS. Yasutomi teaches on page 2284, left column, that:

> Although CTL are likely to play a central role in containing the spread of cell-associated SIV, it may have been naïve to assume that a CTL response with only a single epitope specificity might provide protective immunity against a live virus challenge. Furthermore, CTL recognize endogenously processed viral protein bound to MHC class I molecules on the surface of infected cells (Townsend et al., Cytotoxic T cells recognize fragments of influenza nucleoprotein, Cell,

> 42:457 (1985)). Therefore, such a cellular response might not be expected to contain cell-free virus. Neutralizing antibody is probably needed to achieve sterilizing immunity against cell-free intravenous virus challenge. Therefore, more optimal immunity might be expected from a vaccine that elicits potent neutralizing antibody of broad specificity and CTL with specificities for multiple viral epitopes.

However, it should noted that Yasutomi is discussing protective immunity against cell-free intravenous virus challenge. As this part of the rejection is understood by applicants to be directed to a lack of enablement of "how to use" the invention, it is respectfully pointed out to the examiner that there clearly is utility in stimulating or enhancing a CTL response even if the CTL response in and of itself does not effectively treat a disease. As pointed out by Fox and Yasutomi, CTLs play a prominent role in maintaining the health of HIV-infected individuals and that for a cell-free virus challenge (as opposed to the presence of viruses inside cells), more than a CTL response is needed, such as a humoral response with neutralizing antibodies. One of skill in the art would well appreciate the utility of a method for stimulating or enhancing a CTL response and would readily recognize when and how to use the presently claimed method, such as in combination with a method for eliciting a humoral response. Moreover, it is emphasized that any enhancement or stimulation of a CTL response would be beneficial whether or not it by itself prevents or cures a disease or ameliorates the symptoms of a disease.

Accordingly, the presently claimed invention is enabling to those of skill in the art. Reconsideration and withdrawal of the rejection are therefore respectfully requested.

In view of the above, the claims comply with 35 U.S.C. §112 and define patentable subject matter warranting their allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Claims 1, 6, 7, 8, 17, and 31 have been amended as follows:

1(Thrice-amended). A method of stimulating or ~~modulating~~ enhancing a CTL response to an antigenic molecule in a mammalian subject, comprising administering to said subject an effective amount of a composition comprising an antigenic molecule either entrapped within the interior of an HBsAg particle or exposed or present at the surface of an HBsAg particle, wherein said antigenic molecule is not covalently attached to said HBsAg particle.

6(Amended). The method of claim 1, wherein said antigenic molecule is an antigenic protein or peptide.

7(Amended). The method of claim 10, wherein said antigenic molecule is HIVenv/V3 peptide.

8(Amended). The method of claim 1, wherein said composition further comprises an immunostimulating molecule ~~contained in~~entrapped within or exposed or present at the surface of said HBsAg particle.

17(Twice-amended). A composition comprising an HBsAg particle and a biologically active molecule either entrapped within the interior of an HBsAg particle or exposed or present at the surface of an HBsAg particle, wherein said biologically active molecule is not covalently attached to said HBsAg particle.

31 (Twice-amended). In a method of ~~stimulating or~~

~~modulating~~generating a CTL response to an antigenic molecule in a mammalian subject comprising administering an effective amount of a composition which comprises an antigenic molecule, ~~an~~ the improvement whereby the CTL response is enhanced, wherein said antigenic molecule is either entrapped within the interior of an HBsAg particle or exposed or present at the surface of an HBsAg particle, said antigenic molecule being not covalently attached to said HBsAg particle.